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CONTENTS

THE FRANK E. BUNTS INSTITUTE

The Frank E. Bunts Institute will present, February 25, 26, 27, 1946, a Refresher Course on Treatment on the occasion of the Twenty-fifth Anniversary of the founding of the Cleveland Clinic.

The program of the course is outlined. Because of building alterations facilities will limit attendance to 125. An application blank is submitted for the convenience of those wishing to avail themselves of this course.

Registration will take place at Cleveland Clinic on February 25 from 8:00 to 9:00 a. m.

VASCULAR MECHANISMS OF TERMINAL SHOCK*

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Experience during the war has shown conclusively that treatment of early shock with plasma and blood is satisfactory and demands no more improvement than the perfection of technics. These agents are not as effective, however, in the late, so-called "irreversible" or "terminal" phase of shock. The pressing problem therefore is the study of the nature and treatment of terminal shock.

In its essence, the problem is one of vascular failure; the approach adopted by our groups, first in Indianapolis and later in Cleveland, lay in a study of the reactions of the whole vascular system. These reactions determine the volume and rate of tissue blood flow. They are basic in this study because the degree of tissue perfusion determines the survival of tissues and the survival of vital tissues determines the survival of the shocked patient.

First it is necessary to know something of the relation between the rate of tissue blood flow and the level of arterial pressure.[1] Fortunately, as this study was being undertaken, a patient was seen whose condition all but settled this relationship. At admission, his blood pressure while reclining was 38—0 mm. mercury by auscultation and approximately 30 mm. mercury by intra-arterial puncture. In spite of this, he had few complaints, talked well and clearly, his skin was warm, and there were no signs of shock. Other than extreme hypotension, the only distinct abnormality was failure of urinary secretion. Remarkably, cardiac output was doubled. He failed to show signs of shock because he was able to maintain tissue blood flow by increasing greatly the volume of blood ejected under low pressure into vessels which were not excessively constricted. The abnormality lay basically in a great decrease of peripheral resistance due to the suicidal ingestion of arsenic trioxide. Infusion of angiotonin and fluids seemed in part responsible for recovery so far as hypotension was concerned. Clearly, the level of arterial pressure is not the major determinant of tissue perfusion nor is hypotension coextensive with shock. Rather, the caliber of the arterial blood vessels is a major issue.

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CALIBER OF THE BLOOD VESSELS

The size of arterioles and veins in shocked animals was then ascertained. We and others had observed, although without systematic record, that the arterioles in the eyegrounds of patients in shock seemed constricted. But it was not known whether vasodilatation or vasoconstriction predominated in animals brought into shock by such varied stimuli as burns, limb tourniquets, bleeding, and intestinal manipulation. Indeed, there was at one time a body of opinion in favor of vasodilatation.

The usual methods of microscopic examination of vessels were not applicable in this study because trauma causes locally important changes in circulation.

To solve this problem, working with Dr. Richard Abell, we used the methods of blood vessel observation developed by Clark. Mica windows were placed in rabbits' ears and tissue allowed to grow between them. The blood vessels could then be studied under the higher powers of the microscope without any local tissue irritation. Transparent plastic molds were made for observations on intestinal and mesenteric vessels. These could be inserted a day or more before the observations were made.

As the study began, it was soon clear that vasoconstriction of the new vessels in the ear and of normal mesenteric and intestinal vessels is a constant accompaniment of shock induced by a variety of means.[2,3,4] Moderate vasodilatation appears only about an hour before death. An intense vasoconstriction develops in the renal circulation of dogs during the onset of shock and persists even after blood volume is fully restored by transfusion.[5] In part, this renal vasoconstriction underlies the appearance of crush syndrome or post-traumatic anuria.[6] The spleen of dogs was greatly constricted early in shock, and if the hypotension is prolonged it undergoes a further slow constriction uninfluenced by reinfusion of the withdrawn blood. Thus, direct and indirect evidence establishes the presence of severe vasoconstriction in shock and its persistence until shortly before death.[7,8]

MECHANISM OF VASOCONSTRICTION

The mechanism of this vasoconstriction was then studied. There can be little doubt that during and for a short time after the initiation of shock the vasoconstriction is neurogenic and due to vasomotor reflexes. But, as this brief period of nervous irritation passes off, an ultrafiltrable substance appears in the plasma which, when injected into the vessels of an isolated, perfused rabbit's ear, causes severe and prolonged vasoconstriction.[9] There is therefore good reason to believe that the

persistent, non-neurogenic vasoconstriction of shock is due to the appearance of this substance in the blood. Evidence indicates that it is neither of renal nor adrenal origin but arises from the sites of tissue injury.[10]

REACTIVITY OF VESSELS

We established in 1943 that the pressor response to injection of angiotonin was slightly enhanced in the early phases of shock, but that it weakened as shock deepened and was finally lost at a point when death from sudden vascular collapse was imminent.[11] Extending this study[12] to a variety of pressor (adrenalin, tyramine) and depressor substances (histamine, acetylcholine), it became evident that in burn shock three phases of reactivity could be clearly defined: (1) the injury phase, a brief one during the period of burning in which arterial pressure rises and the phenomena are those of acute nervous excitation; (2) the transitional phase during which arterial pressure falls moderately and the response to pressor drugs is often, but not always, enhanced; and (3) the terminal phase during which the responses, both pressor and depressor, are reduced and finally fail. Cardiometric studies showed that this refractoriness arises not only in peripheral vessels, but in the heart as well.

Shock due to bleeding does not exhibit the phase in which enhancement of the response to adrenalin occurs. Partial refractoriness appears early and may persist for several hours until it becomes complete, even with strong concentrations of adrenalin. Usually restoration of the blood only partially restores this response.

Clearly then, the terminal phase of shock may be partially characterized as a state of vascular and myocardial refractoriness to chemical stimulation. It seems the vascular tree is robbed of its ability to respond rapidly and accurately to the demands placed upon it. In this vulnerable condition stimuli which of themselves seem insignificant—such as the removal of 50 or 100 cc. of blood from a large dog—may immediately precipitate vascular collapse and death.

Two other phenomena of considerable interest were observed. With Dr. K. G. Kohlstaedt experiments were done in which the heart was placed in a cardiometer, so that its volume and excursions could be recorded with the thorax closed. In these, progressive bleeding led to reduction in the size of the heart shadow as seen by x-ray. As the terminal phase approached, instead of further shrinkage, the heart progressively dilated, as did the peripheral vessels. Cardiac, as well as peripheral vascular failure, therefore, is another characteristic of terminal shock due to bleeding (fig. 1 and 2).
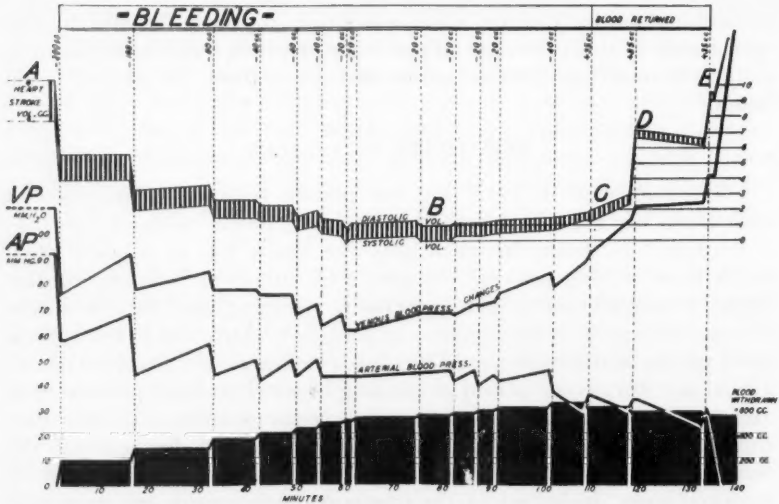
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FIG. 1—Schematic diagram of the effect of hemorrhage and prolonged hypotension on circulatory dynamics. A, Cardiometer record of stroke volume in prehemorrhagic period. B, Point of greatest reduction of diastolic and systolic volume. C, D, and E, 35 cc. of blood injected intra-arterially. VP, Intra-thoracic venous pressure in millimeters of water. AP, Arterial pressure in millimeters of mercury. Shaded area denotes total amount of blood removed (scale at right side). Scale at upper right indicates stroke volume units of cardiac dilatation. (Courtesy of SURGERY 16:430, 1944)

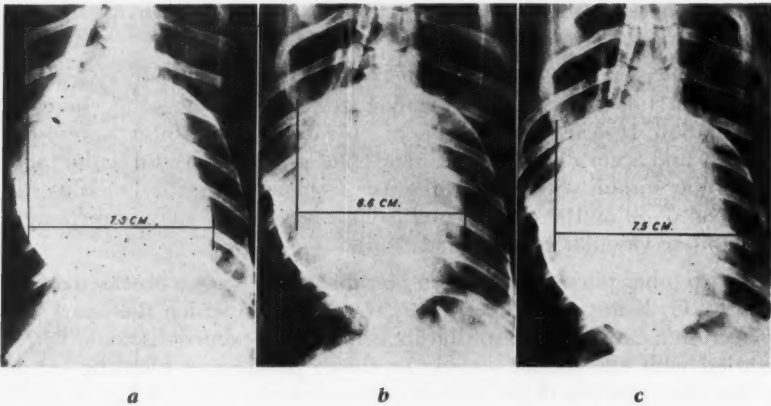FIG. 2—X-ray photographs taken before and during prolonged post-hemorrhagic hypotension. (a), Photograph of roentgenogram taken during prehemorrhagic period. (b), Photograph taken during hypotensive period when cardiometer indicated greatest reduction in cardiac size. (c), Photograph taken just before treatment began. Cardiometer indicated an increase of 3.5 stroke volume units in systolic volume. (Courtesy of SURGERY 16:430, 1944)

The second phenomenon concerns the rate at which blood flows into a shocked animal when the arterial pressure is maintained by connecting a larger artery to a reservoir of blood under the desired pressure. Blood will flow in or out according to the variations of the animal's blood pressure and, presumably, the capacity of the blood vessels and reservoirs. Such an animal may live for several hours at a low level of arterial pressure in spite of persistent vasoconstriction. But the approach of the terminal phase, which, as we have seen, is heralded by vascular and cardiac dilation, may also be gauged from a sudden inflow of blood from the reservoir.

Chambers, Zweifach, Lowenstein, Schorr, and their associates have arrived at somewhat similar conclusions concerning the state of the very smallest arterioles (the metarterioles) in shock, although from an entirely different approach. The metarterioles of the exteriorized meso-appendix of rats are measured under the microscope. Sensitivity to adrenalin contained in the fluid bathing the tissue is estimated roughly by the degree of constriction which occurs. Early in hemorrhagic shock the response is greatly heightened, while late, refractoriness appears along with what they term loss of vasomotion. As described above, we have not found after hemorrhage a phase of enhanced pressor response to adrenalin.

THERAPEUTICS OF TERMINAL SHOCK

The experimental data make it clear that once vascular and cardiac refractoriness appears in shock, vascular collapse is imminent, and at present such collapse is irremediable. But it generally takes a long and variable time for this state to develop. A method which would rapidly restore arterial pressure so that, in spite of vasoconstriction, the perfusion of tissues would be adequate for survival—and here the cardiac and cerebral beds should be considered—would have much to recommend it.[13]

Such a method was suggested to us by Seeley and the experimental evidence obtained in work with Dr. K. G. Kohlstaedt and, more recently with Dr. Otto Glasser.[14] The method consists in the rapid administration of blood into a large (radial or femoral) artery under positive pressure. For example, if the patient's blood pressure be taken as 30 mm. mercury and the duration of shock not such that total vascular irresponsiveness would be present, a number 18 needle is inserted into the artery with the point toward the heart, and blood is administered freely from a reservoir set at 50 mm. mercury. When equilibrium is reached at this pressure so that inflow ceases, the positive pressure is increased to 70 mm. mercury and so on by increments until the final equilibrium of

arterial and reservoir pressure is reached at a pressure of approximately 100 mm. mercury. This point should be reached in a few minutes.

If it were believed that vascular refractoriness appeared because of a long period of deep shock, it sometimes seemed desirable to give a small amount (200 mg.) of 2-amino heptane into the infusion tubing just as the blood started to flow in. The drug is used because it tends to constrict the heart and, as has been shown, cardiac dilatation is a serious danger in this stage of shock. The drug has no use apart from the co-incident infusion of blood or plasma, and repeated doses are increasingly ineffective. It has not been shown to have value in the treatment of terminal shock either alone or in conjunction with intravenous transfusion.

The intra-arterial infusion method has several advantages. These seem to be: (1) the delivery of blood into the aorta perfuses the coronary vessels, relieving myocardial ischemia, and since myocardial ischemia probably underlies the cardiac dilatation and insufficiency, places the heart rapidly in a state in which it can pump the infused blood to other areas; (2) when, before the infusion, the patient may have been apneic, at its start he will take a deep breath, as if the arterial filling had rapidly extended to the vital medullary centers; (3) in contrast with intravenous

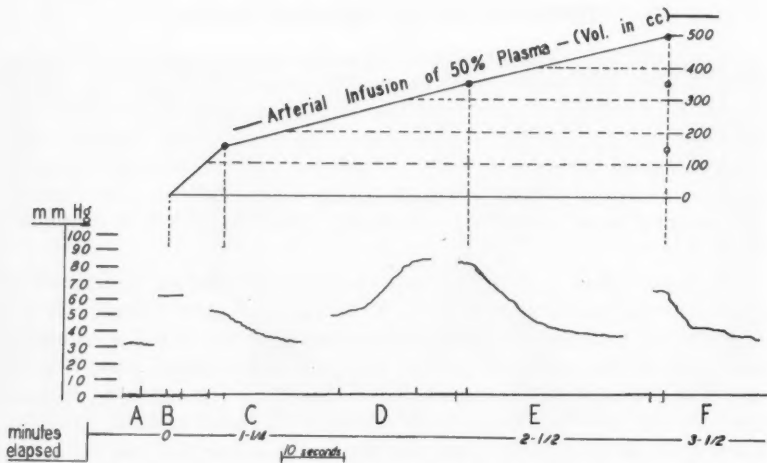FIG. 3—Example of the effect of intra-arterial infusion in a patient in deep shock with undiagnosed abdominal bleeding. Arterial pressures are recorded on a kymograph. A, Initial pressure. B, During intra-arterial infusion. C, Infusion discontinued and pressure fell off rapidly. D, Reinstituted. E, Infusion stopped. F, Same sequence repeated. Clearly blood was leaking rapidly from the vascular tree. (Kohlstaedt and Page)

transfusion, blood pressure is rapidly restored, and the volume of blood infused is determined, not by time-consuming analyses or by guess, but by the actual capacity of the vascular tree; and (4) a subsidiary advantage lies in the fact that latent bleeding (spleen, liver, kidney), which causes arterial pressure to fall off rapidly, is detectable within minutes rather than hours (fig. 3).

Possibly the most important advantage of the method lies in the emphasis it places on the need for speed in the treatment of severe shock. Untold lives would be saved if physicians thought of the treatment of shock in terms of minutes rather than hours.

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OBSCURE, INCARCERATED, OR STRANGULATED HERNIA AS A CAUSE OF INTESTINAL OBSTRUCTION

A Report of Four Cases

T. E. JONES, M.D., AND R. W. KEHM, M.D.

The diagnosis of acute intestinal obstruction in most instances is readily established. Symptoms of pain, vomiting, and failure to pass gas or feces are usually the classical triad. In addition, systemic reaction and physical findings make the diagnosis conclusive.

The etiologic factor in such cases, however, often presents a difficult problem and one that must be decided as soon as possible. Unless surgical intervention is timely, the rapid sequence of incarceration, strangulation, mesenteric thrombosis, transudation of bacteria through the intestinal wall, peritonitis, and death will follow.

Causes of acute intestinal obstruction are innumerable. Infants are apt to have congenital anomalies, and intussusception occurs often in the first year of life. In children acute intestinal obstruction commonly results from intussesception, band adhesions, adherence of the intestine to infected retroperitoneal glands, undiagnosed appenc.icitis, and hernia. Common causes in adults are tumors; and in the aged, incarcerated hernia and malignant tumor. Many of the rare causes of intestinal obstruction must also be kept in mind.

Incarcerated hernia obstructs the fecal flow. Strangulated. hernia impairs the blood supply as well and is usually present when the hernial tumor is painful and tender to touch. The type of acute intestinal obstruction with which this report is concerned is the obscure and frequently undiagnosed incarcerated or strangulated hernia.

Incidence. In the past six months 3 such cases have been successfully operated upon, and 1 patient died before surgical intervention. Although before operation hernia was suspected in each case except the second, in no case could incarcerated or strangulated hernia be determined as the direct cause of the obstruction.

CASE REPORTS

Case 1—A man, aged 51, developed acute abdominal pain, followed by nausea and vomiting two days before admission to the hospital. He was unable to expel gas or stool.

Abdominal examination revealed typical layered appearance of small bowel distention with obstructive bowel tones on auscultation. The patient had no history of

hernia, previous operation, or gastrointestinal bleeding. A small nodule, the size of a pecan in the left femoral region, was not tender, had consistency of a lymph node, and transmitted no tactile pulsation. The patient said that the nodule had been present ten years, never grew larger, or caused discomfort.

Study of gas shadow by x-ray did not localize the point of obstruction. A Miller-Abbott tube was passed through the nose, and patient was supported with parenteral fluids until well hydrated. Exploration through a rectus incision revealed a small knuckle of ileum incarcerated in the left femoral canal. It was mobilized with some difficulty and the hernia repaired. The patient recovered.

Case 2—A man, aged 84, was well until one week prior to admission. Following a hearty meal he had developed acute epigastric pain followed by nausea and vomiting, which continued intermittently for six days.

The patient was dehydrated, with stercornaceous breath and toxic facies. The abdomen was distended with only a few tinkling sounds on asucultation. Proctoscopy was negative for 25 cm. Retrograde x-ray studies were negative for colonic obstruction. The patient had a right inguinal hernia, easily reduced, which had been present "for years." There was no clinical evidence of incarceration or strangulation.

The patient became irrational so that a Miller-Abbott tube could not be used. Supportive measures were instituted, but the patient developed auricular fibrillation and expired before an operation could be performed. Autopsy revealed a small knuckle of ileum, twisted, strangulated and adherent at the internal ring, with associated mesenteric thrombosis.

Case 3—A man, aged 69, developed pneumonia six weeks prior to hospital admission. He convalesced uneventfully until the fifth week when he developed epigastric pain, nausea, and vomiting. Vomiting became fecal in nature and he was unable to retain food or liquids.

Patient was dehydrated with clinical evidence of intestinal obstruction. A small, soft lump palpable in the left femoral region, was not tender and showed no evidence of incarceration or strangulation. The patient did not know exactly how long the tumor had been present, but thought it was for some time. Exploration through a rectus incision revealed that a small knuckle of ileum incarcerated in the left femoral canal was causing the obstruction. Convalescence was uneventful. It was believed that the coughing associated with pneumonia caused the incarceration.

Case 4—A woman, aged 77, developed acute epigastric pain followed by nausea and vomiting, three days before hospital admission. She had no history of hernia, but had a hysterectomy twenty-five years ago.

Patient was dehydrated with clinical evidence of intestinal obstruction. A soft, slightly tender mass in the right inguinal region suggested femoral hernia. There was no certainty, however, that it was not an intra-abdominal mass. Surgical exploration over the mass revealed a partially strangulated loop of ileum impacted in the femoral canal. Since the serosa still had luster and the bowel showed evidence of increased vascularity after reduction, the bowel was replaced in the abdomen and the hernia repaired. Convalescence was uneventful.

SUMMARY

In the 4 cases of intestinal obstruction caused by obscure, incarcerated, or strangulated hernia diagnosis seemed simple after operation or autopsy revealed the true pathology.

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Actually each instance presented a difficult diagnostic problem. In not one case could an absolute diagnosis of hernia as the cause of the obstruction be made, although hernia was suspected in all but the second case.

In any occasion of acute, intestinal obstruction where there is a history of previous hernia or any masses in the inguinal or femoral region, the possibility of strangulation with incarceration of the hernia should be excluded.

The incision should be in a region where the suspected hernia is easily accessible. Decision as to where the incision should be made, however, is often difficult when the etiologic factor is not localized.

Clinical diagnosis of high or low obstruction may help since the jejunum and proximal portion of the ileum usually lay high in the abdomen and to the left, while the distal portion of the ileum is apt to be in the lower part of the abdomen or pelvis. In the first case there was some difficulty in freeing the incarcerated bowel because the incision was distant from the site of herniation.

A small incision is preferable. It may be enlarged if indicated. Through a small wound a collapsed loop of intestine can be picked up and traced back to the point of obstruction. A large incision presents the problem of coping with an open abdomen full of distended loops of bowel. With a small incision shock from exposure and handling is minimized, and closure of the wound is greatly facilitated.

ABSENCE OF PITUITARY FAILURE
IN FAT BOYS WITH TESTICULAR DEFICIENCY

E. PERRY McCULLAGH, M.D., AND IRENE T. KLINE, M.A.

The term Fröhlich's syndrome is commonly used to designate obesity and retarded sexual maturation without regard for the fact that the original description of the condition by Babinski[1] and by Fröhlich[2,3] included also the presence of a suprasellar tumor. While obesity and retarded maturation are a combination frequently seen, suprasellar tumor is a rare concomitant. Adiposogenital dystrophy, a term proposed by Bartels,[4] might be used appropriately for these more common cases without tumor were it not that it, too, was originally designed to include the presence of a suprasellar tumor.

Opinions on the testicular biopsies are based on reports of Dr. Earl T. Engle, who studied the sections.

Early workers[4,5,6] pointed out that obesity could not result from pituitary failure. This fact has been repeatedly confirmed. Bailey and Bremer[7] were the first to prove experimentally that a condition simulating adiposogenital dystrophy could be caused by a lesion in the hypothalamus alone, without injury to the pituitary gland. Substantiation of this concept has been abundant.[8] The implication has remained, however, that the lack of pituitary gonadotrophins is the explanation of the gonadal deficiency in patients who are usually designated as having adiposogenital dystrophy. In cases of tumor in the region of the pituitary gland this supposition is undoubtedly true. Suprasellar tumors in boys are uncommon. When such a tumor occurs, it is likely to be associated with normal or less than normal height. The genitalia may be relatively infantile, but such patients are seldom obese.

Fröhlich's patient was approximately 58 inches (145 cm.) in height according to Bruch's estimate[3] (no definite height was originally given) and was 118.8 pounds (54 kg.) in weight at the age of 14 years, which was approximately 30 per cent over ideal. The tumor in the pituitary region, the presence of which was proved at operation, was apparently a craniopharyngioma. On the other hand, the common phenomenon of testicular failure in adolescent boys is generally not associated with a tumor in the region of the pituitary gland. Those patients without pituitary tumor may be above average height; they do have various degrees of hypoplasia of the genitalia, and their obesity is frequently greater than that in patients with a tumor. In short, Fröhlich's syndrome in its true form is very rare, and the term as it is usually used is a misnomer.

Gonadal failure with obesity is diagnosed more frequently in boys than in girls largely because the external genitalia can be seen to be small, or may seem to be small, because of excess of surrounding fat; and because the normal physical activity and aggressive attitude of the adolescent boy is replaced by a somewhat feminine demeanor and often by a distinct tendency to placidity or laziness. The condition must be carefully distinguished from simple obesity. In fat girls the condition may be suspected when there is delay in breast development and delay in the appearance of the menses. In adolescent girls who are not fat delay in breast development and retarded appearance of such changes as fullness of the hips make ovarian deficiency more evident. Minor degrees of gonadal failure, however, are not easily determined in either sex during early adolescence, since wide variations are normal.

Hypothyroidism is commonly misdiagnosed upon the finding of low metabolic rates in these obese children with delayed adolescence. Such patients frequently show no other signs of hypothyroidism. Their skin

DIAGNOSTIC CHARACTERISTICS		CASE I		CASE 2		CASE 3	
		Before treatment. 14 yr. 3-8-44.	After treatment, 15¾ yr. 12-3-45.	Before treatment 10½ yr. 6-23-44	After treatment 11¼ yr. 10-6-45	Before treatment 18 yr. 1-5-45	After treatment 18½ yr. 5-4-45
HYPOGENITALISM	Assays — Urinary Gonadotrophins	105-212 MU/24 hr. 3-8-44; 105-212 MU/24 hr. 9-11-44.	53-105 MU/24 hr. 1-11-45. (no injections previous 2½ wk.)	212-318 MU/24 hr.	6-13 MU/24 hr. 7-27-45 (no injections previous 2 wk.)	105-212 MU/24 hr.	not done
	Urinary 17-keto-steroids	2.2 mg./24 hr.	5.8 mg./24 hr. 1-22-45.	1.5 mg./24 hr.	highest assay after 6 mo. therapy: 1.3 mg./24 hr.	7.8 mg./24 hr.	3-31-45 6.4 mg./24 hr.
	Testes — Location and size	L: about 3x1.5 cm. in scrotum R: severely atrophied	L: normal R: still small, but in upper scrotum	about 1.5x0.75 cm. approximately at external ring; both drop into scrotum	normal	about 1.5x1.25 cm. in scrotum	unchanged
	Biopsy	8-12-44, L.: "Progressive tubular fibrosis with spermatogenic arrest"		9-12-44 "Very early developmental arrest, bilateral, with complete lack of differentiation"		1-26-45 "Incomplete development bilateral with beginning tubular fibrosis and cellular atrophy"	
	Penis Size	2.25 cm. long	normal; 6.75 cm. in length	small	normal	7 cm. long; with long prepuce; normal for age 12	9 cm. long
OBESITY	Height[1] (inches)	68 (avg. 62.2)	71¼ (avg. 66.2)	58¾ (avg. 54.8)	60¾ (avg. 57.5)	65½ (avg. 68.2)	66 (avg. 68.2)
	Weight[1] (pounds)	209 (134 ideal for h.)	225 (155 ideal for h.)	131 (77 ideal for h.)	106½ (85 ideal for h.)	155½ (136 ideal for h.)	150 (136 ideal for h.)
	Overweight[1] (pounds)	75	70 (did not follow diet)	54	21	19½	14
	Distribution of fat	feminine fat distribution	less suggestion of feminine configuration	abdomen, hips, mammary glands	normal except for slight "pot belly"	especially in face, abdomen, hips and breasts — perhaps gynecomastia	little change
HYPOMETABOLISM	Basal metabolic rate	−18%	−16%	−13% 6-27-44	−23% 8-1-45	−12%	slight increase
HYPOTRICHOSIS	Pubic hair	none	normal for 17 yr.	none	beginning	½ normal female	no change
	Axillary hair	none	½ normal	none	none	very scant	no change
	Facial hair	none	slight mustache and beard	none	none	none	
FAULTY SKELETAL DEVELOPMENT	Epiphyseal age	not estimated		10 yrs.	not repeated	not estimated	
	Span exceeds height by	2 inches		0 inches			
SUBJECTIVE SYMPTOMS	Facies	immature for age	much more mature	puerile	more mature	puerile	same
	Demeanor	distinctly unaggressive	improved	alertness below normal	more alert	less aggressive than normal	improved
	Activity	much below normal	improved	good average endurance	more active	moderate	slightly more active
	Voice	puerile	distinctly lower	puerile	puerile	puerile (high)	same
THERAPY	Chorionic Gonadotrophin	500 IU q 2nd day to 750 IU daily (except 2½ weeks) 3-6-44 to 5-1-45		50 IU q 2nd day 6-27-44 to 2-9-44; 500 IU/day 2-5-45 to 3-10-45; 500 IU 3xwk. 3-10-45 to 7-14-45		3 months 2-10-45 to 5-4-45; 750 IU q 2nd day	
	Thyroid	Gr. 1 daily 3-6-44 to 6-8-44; Gr. 2 daily 6-8-44		Gr. 1 daily throughout		Gr. 1 daily throughout	
	Diet	1200 cal. per day (followed poorly)		1400 cal. per day until 6-14-45 later, 1800 cal. per day		1200 cal. with 60 Gm. protein per day	

[1] From Baldwin, B. T. and Wood, T. D.: Weight-Height-Age Tables in English Units of American Born Boys (clothed) of School Age. (Iowa: The Iowa Child Welfare Station, State University of Iowa, 1931).

is fine, and their complexions are pink. Their teeth may be excellent. Their nails grow well. Their height is normal; their bone age is little, if at all, retarded, and their blood cholesterol is typically within normal range.

The usual conception of the physiologic mechanism involved in adolescent hypogonadism with obesity is that there is a lack of pituitary sex hormone production accompanied by a possible hypothalamic disorder. The latter is suggested more forcefully when hunger, thirst, drowsiness, and a lowered metabolic rate also are present. A clear demonstration of disturbance of hypothalamic function is impossible without suprasellar lesion. The belief that there is a deficient production of pituitary sex hormone has been supported by the fact that many patients of this type without pituitary or suprasellar lesions respond dramatically to adequate doses of chorionic gonadotrophin. Furthermore, gonadotrophins could not be found in the urine of any untreated cases by Nathanson and Aub.[9] The discrepancy between their findings and ours (table 1) is probably because we have employed a more sensitive assay method.

In the past few years we have become increasingly convinced that deficiency of pituitary sex hormone is not a usual part of this syndrome of obesity and hypogonadism. Many such persons, if untreated, may eventually respond to natural stimuli and attain normal adulthood,[10] suggesting that the pituitary gland in those who undergo spontaneous cure is, in time, capable of stimulating the gonads to a normal response. This spontaneous cure seems to be particularly possible for the patients whose weight is brought to normal.

In a group of our untreated adolescent boys with evidence of hypogonadism and varying degrees of obesity, titres of urinary gonadotrophins equal to or above those of normal adult males are present (tables 1 and 2). The studies of Greulich et al.[11] have shown that the urinary

TABLE 2
Urinary Gonadotrophin Titres
Normal Adult Males

| MU/24 hr. | | No. of Cases |
More Than	Less Than	
26	53	12
53	105	9
105	212	2
		Total 23

a   *b*

FIG. 1, Case 1 (a) Before treatment. Age 14 years.
(b) After treatment. Age 15 years, 9 months.

excretion of gonadotrophins in normal adolescent boys reaches an adult level at 14 years of age, if skeletal development and secondary sexual

14

a   b
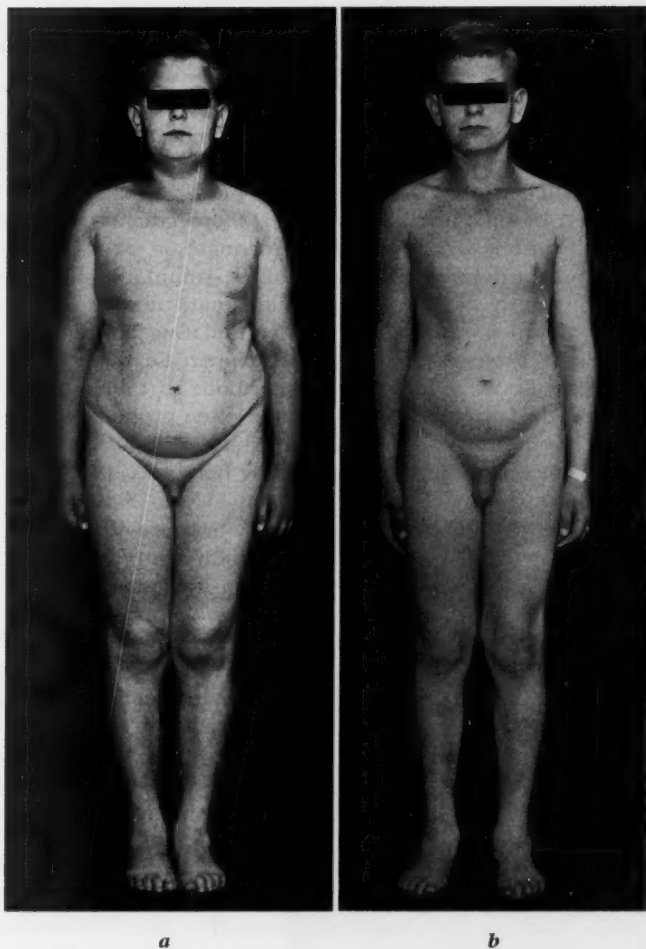
FIG. 2, Case 2 (a) Before treatment. Age 10 years, 6 months.
(b) After treatment. Age 11 years, 6 months.

characteristics have attained a corresponding level of maturity.

The method we used for urinary gonadotrophin assays is the mouse uterine weight method described by Klinefelter *et al.*[12] Each test was done on a 16 hour aliquot of a 24 hour specimen. Normal adult male titres determined by this method in our laboratory are given in Table 2.

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Urinary 17-ketosteroid determinations[13,14] were done on 24 hour or 72 hour urine specimens and expressed as mg. per 24 hours. Table 3 shows normal adult male tires for comparison.

The first explanation which comes to mind with regard to the excess titres of gonadotrophin in boys with obesity and genital dystrophy is that they have some degree of primary hypogonadism, or in milder cases a low testicular responsiveness, which may eventually attain relative normality. In some instances, however, these patients do respond to injections of chorionic gonadotrophin. Adequate or excessive amounts of urinary gonadotrophin, measured as follicle-stimulating hormone, do not necessarily imply the presence of an adequate amount or an excess of luteinizing hormone or interstitial cell-stimulating hormone. It does not seem likely, however, that there is an increase over the normal quantity of interstitial cell-stimulating hormone or even a lack of responsiveness to it, because of a prompt and often pronounced response to injections of chorionic gonadotrophin, which contains chiefly luteinizing hormone or interstitial cell-stimulating hormone.

Three adolescent boys (figures 1, 2, and 3) who have obesity and testicular deficiency with absence of pituitary or suprasellar tumor, and who might ordinarily be designated as Fröhlich's syndrome or adiposogenital dystrophy, are selected to demonstrate these points (table 1). It will be noted that two of these patients who had high titres of urinary gonadotrophin appeared to respond to injections of chorionic gonadotrophin. Their own gonadotrophins evidently were not producing the interstitial cell stimulation which was brought about by the pregnancy urine extract used in treatment.

Testicular biopsies performed in these and similar cases reveal that there are at least in some cases varying degrees of developmental arrest of the tubular tissues. There are also fibrosis of the intertubular tissues, varying from mild to severe, and a less than normal number of interstitial cells. Such studies will be presented subsequently in greater detail.

Wherever large amounts of follicle-stimulating hormone are present in the urine, pituitary dysfunction may be said to exist. Theoretically it is possible that there may also be a deficient production of luteinizing hormone, but until a satisfactory method for its measurement is available, that possibility cannot be ascertained. As an explanation of the hormonal imbalance the following might be considered: a primary pituitary disorder creates an excessive production of follicle-stimulating hormone, thereby causing testicular damage. It is more likely, however, that the main defect lies in early developmental arrest of the testis itself and that pituitary hyperfunction or dysfunction results as a secondary result of this change.

TABLE 3
Urinary 17-Ketosteroid Titres
Normal Adult Males

Mg./24 hr.	No. of Cases
4.0-4.9	1
5.0-5.9	1
6.0-6.9	4
7.0-7.9	7
8.0-8.9	6
9.0-9.9	6
10.0-10.9	4
11.0-11.9	5
12.0-12.9	1
13.0-13.9	2
14.0-14.9	2
15.0-15.9	0
16.0-16.9	1
17.0-17.9	1
18.0-18.9	1
Mean:	Range:
9.0-9 9	4.8-18.4 mg/24 hr. Average: 9.5 mg./24 hr.

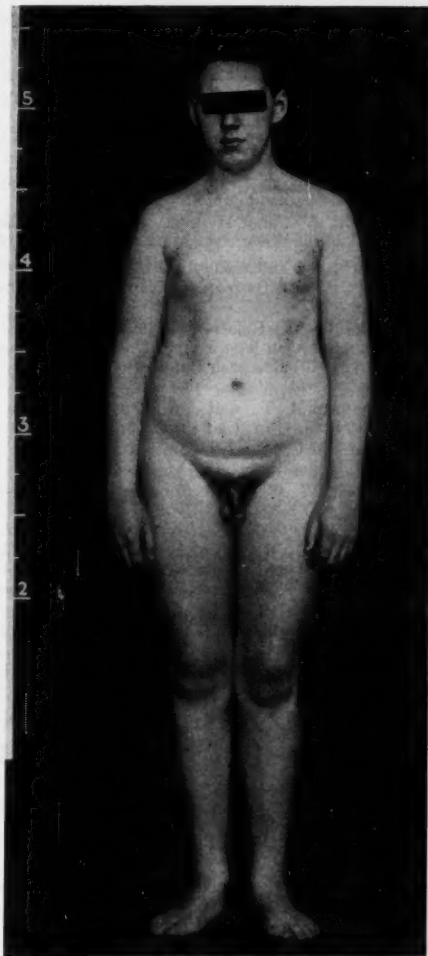FIG. 3, Case 3—Before treatment. Age 18 years.

SUMMARY

An outline of the essential findings in three patients is presented. These patients represent a group now being studied whose primary features are testicular failure of the adolescent type, obesity, absence of tumor in the region of the pituitary gland, and the presence of a normal or an increased quantity of follicle-stimulating hormone in the urine.

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CERVICAL PERIARTHRITIS

Diagnosis and Treatment

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The term, periarthritis, by definition means inflammation in the tissues around a joint. Every case of arthritis has an associated periarthritis. The term, cervical periarthritis, we have reserved for those cases in which no arthritis or other abnormal anatomical bone change can be demonstrated. It may be the cause of pain and stiffness in the neck and is usually recognized by the presence of soreness in the supporting ligaments and muscles of the neck.

Many patients with cervical periarthritis complain of numbness and aching in the arms and hands and may have soreness in the shoulder muscles. In the absence of x-ray evidence of disease in the bone, the

* Assistant in Medicine.

finding of muscle tenderness and painful limited motion in the neck usually identifies the neck as the cause of trouble.

Cervical periarthritis may be associated with functional conditions of the spine, such as scoliosis and relaxed posture. It may be part of the generalized rheumatic involvement of periarticular structures commonly called chronic fibrositis. In some cases, exposure to cold and febrile diseases such as influenza may be important etiologic factors.

The conditions which are considered in the differential diagnosis of cervical periarthritis are osteoarthritis of the cervical spine which is shown on x-ray, and subdeltoid bursitis demonstrable on physical examination or x-ray. Less commonly, one has to differentiate rheumatoid arthritis in the cervical spine, ruptured intervertebral disc,[1] hypertension, scalenus anticus syndrome,[2] cervical rib,[3] and rarely, neoplasm either in the cord or with metastasis in bone.

TREATMENT

Treatment of cervical periarthritis is directed to relaxation of the neck muscles, breaking up of fibrositic nodules when present, stretching of the fascial tissues, and increasing the width of the vertebral foramina. In our experience we have found the combined use of local heat (usually short wave diathermy), massage, stretching, and progressive exercises effective in relieving the patient. These treatments are given two or three times a week and may be supplemented with home treatments. The total number depends on the patient's response.

The patient, stripped to the waist, rests comfortably on a padded table. Short wave diathermy is applied to the neck, including the upper fibers of the trapezius muscles, for 20 to 30 minutes. At times it is necessary to lower the intensity of the diathermy since some patients have increased muscle pain when treatment is started. If the patient does not tolerate short wave diathermy, infra-red may be substituted.

Heating is followed by massage in the direction of the venous flow. Massage is light at first, increasing in depth depending upon the acuteness of the symptoms and the patient's tolerance. Vigorous massage is contraindicated as it may increase the symptoms. The massage, however, should be deep enough so that after a varying number of treatments fibrositic nodules may be broken up. It is necessary that the therapist allows the feel of the tissue to guide him in the depth of massage.[4]

The patient then sits in a stable chair. By means of the active exercises illustrated in A, B, and C the range of motion is determined. The therapist then manually stretches the neck and assists the patient in increasing his range of motion. The amount of assistance that can be given will be determined by experience. Care should be taken not to
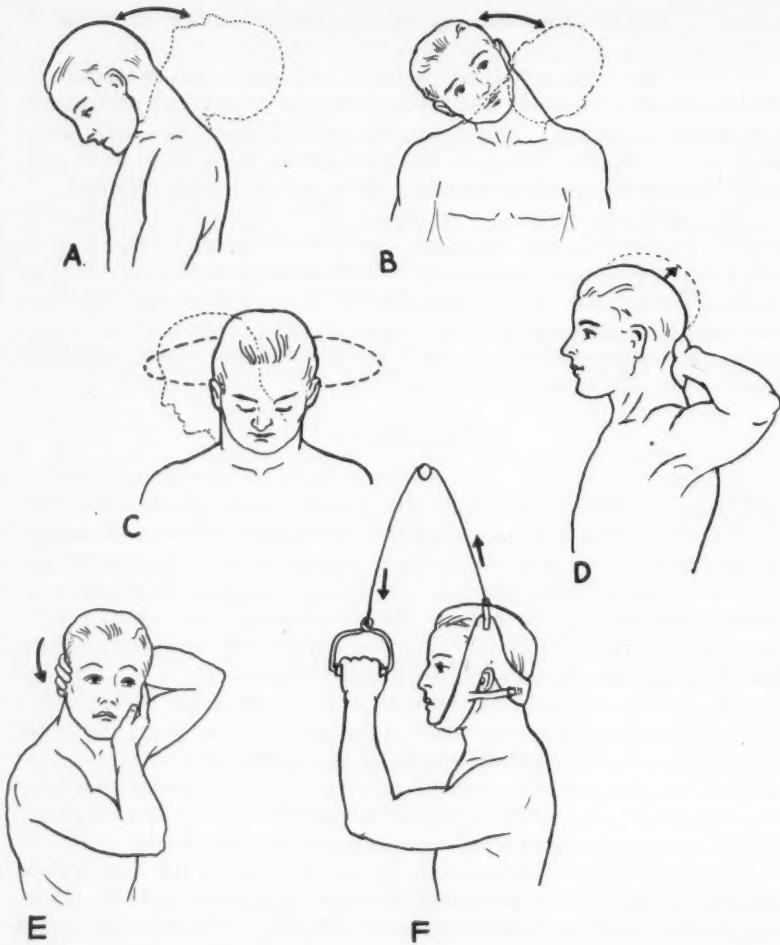
attempt to progress too rapidly in the exercises at this point. Finally, the patient moves his head against the resistance of the therapist's hand.

Stretching and assistive exercises are repeated with the aid of a head sling such as the Sayre type. The patient raises the buttocks about one inch from the chair, the sling is made taut by means of a windlass and ratchet, and he then allows his weight to fall against the resistance of the sling. This stretching is usually not difficult and most of the weight is carried by the chair and only part by the sling. Assistive exercises are

again repeated. The patient then stands and rises on his toes while the sling is made taut. The weight is thus divided between the heels and the sling when his feet resume the anatomical position. Assistive exercises are repeated. Stretching by means of the sling is repeated two to three times in each position.

Local heat and exercises are essentials of home treatment. The patients should be instructed in the use of a firm bed for sleeping and postural correction. Satisfactory local heat may be obtained at home from an electric heating pad or hot water bottle. The patient should be taught to exercise his neck first actively as illustrated in A, B, and C, and then with the assistance of his own hands attempt to increase range of motion where limitation exists. Finally, he should learn to exercise against resistance as illustrated in D and E. Frequently it is advisable to instruct the patient in the use of a sling for home treatment as in F of the figure.

When the patient is not able to have a full course of treatment by a trained therapist, home treatment may bring about complete relief. Furthermore, these patients are subject to recurrence of symptoms and if they are familiar with the use of heat and exercises they may find early relief. Treatment, of course, is most effective in the early stages, since it prevents the fascial tissue stiffness encountered in the cases of long duration.

The following case is illustrative of cervical periarthritis and its response to treatment.

CASE REPORT

A woman, aged 32, complained of episodes of pain in the back of the neck. This pain was frequently worse with fatigue and was associated with radiation into the occipital area and down between the shoulder blades. On several occasions, the patient had noticed a poorly localized numbness in the hands.

Physical examination revealed the patient to be of normal habitus. Blood pressure was 110/75 mm. Hg and heart and lungs were normal to percussion and auscultation. Skeletal examination revealed a relaxed posture with increased lumbar and cervical curves. There was moderate restriction of rotation of the neck and pain on passive extention of the neck. Palpation of the deep muscles of the neck revealed tenderness extending down to the level of the fourth dorsal vertebra.

The laboratory reported a normal blood count, and x-ray examination of the cervical spine revealed no abnormal bone or joint changes. Clinical impression was cervical periarthritis associated with postural strain.

The patient was started on physical therapy as described. She was given treatments twice a week supplemented by daily postural exercises and exercises to the cervical spine at home. The patient noticed immediate improvement, and after four treatments her symptoms entirely disappeared. Follow-up observation in four weeks revealed no return of symptoms.

PHYSIOLOGIC BASIS

The physiologic basis for this treatment is not well documented by experimental data. It appears that the first effect of local heating is on the sensory nerves. The patient is more comfortable and there appears to be a certain amount of neurogenic relaxation. There may be a reflex relaxation of the muscles supplied by the same segment supplying the skin area which is heated. Through sympathetic nerve stimulation there is a general vasodilatation as shown by increased skin temperatures at distant parts. Locally, the capillary dilatation is more marked, apparently because of the direct effect of increased temperature on the capillary walls.

The effect of heat on the muscles is primarily through the increased circulation.[5] It has been shown that the flow in a limb exposed to temperature of 42 C. is on the average five times as great as when exposed to temperatures of 26 C.[6] On the other hand the external application of heat simulates a depression in the general metabolism.[7] It is true that raising the temperature of the tissues will increase the local metabolic rate. The total change in temperature of the muscular tissues after diathermy, however, has been shown to vary from 2 to 4 C.[8] In a living externalized heart of a cold-blooded animal a rise in temperature of 10 C. results in an increase in metabolism of two to three times.

It can be seen, therefore, that the increase in circulation is far in excess of the small increase in metabolism that may occur, and metabolites can be literally washed out with reduction in the irritability of the muscle.

Light massage in direction of the venous flow increases local circulation still further, and the effect of light stroking on the nerve endings enhances the neurogenic relaxation.

Deep massage, as described, softens the stiffened fascial tissue and breaks up fibrositic nodules if present. Stretching widens the intervertebral foramina with relief of paresthesias due to inflammation or possible pressure on nerve roots. Frequently, immediate relief of numbness and tingling in the hands, when present, follows the first manual stretching of the neck.

Exercises re-establish normal joint motion. Muscles made weak by inflammatory processes and disuse are strengthened by active motion and by working against resistance.

Although physical therapy is of first importance, attention should be given to elimination of causative factors and treatment of the generalized disease when present. Frequently, diet therapy and general regulation of the patient's activities is important. Fatigue states must be eliminated. Extremely important are the correction of faulty body mechanics and

posture. Exercises for posture training should be a part of every physical therapy program for patients with cervical periarthritis.

Eye strain which may be associated with cervical periarthritis is the type due to extra ocular muscle imbalance. Neck muscles have been thought of as accessory eye muscles. In cases of weakness in some of the intra-orbital extra ocular muscles, compensatory stresses may be placed on the posterior muscles of the neck. Abolishing these stresses by means of proper exercises and lenses may be beneficial.

Occupational factors must be considered. Students, draftsmen, and bench workers, for instance, may suffer because of prolonged tension on posterior neck muscles associated with leaning over their work.

In acute cases of cervical periarthritis without other associated diseases, intravenous iron in the form of iron cacodylate every two or three days may be a valuable adjunct to physical therapy. The use of salicylates is common practice and needs no comment. Occasionally, codiene or demerol may be necessary for one or two days while physical therapy is being started.

Mention should be made of the technic of local infiltration of anaesthetic drugs. Infiltration is directed into painful nodules when present and some outstanding results have been obtained especially in cases with associated neuralgic head pain.[9] This technic may be used in conjunction with physical therapy in selected cases.

SUMMARY

The objective findings in patients with cervical periarthritis may be meager. The discomfort and the disability associated with this condition may be great. Each patient should be treated carefully and thoroughly with particular attention to the local disease, and the important occupational and postural factors. Relief of symptoms will then be the rule with few exceptions.

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EDEMA II
CLINICAL SIGNIFICANCE

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It is the purpose of this paper to outline the clinical syndromes in which edema significantly appears, to discuss their differentiation, and to comment on the changes to which edema itself may give rise. The frequency with which edema occurs indicates the variety of its origins. Its physiologic bases have been reviewed in a former paper.[1]

Conditions in which edema commonly appears are summarized in Table 1. Although clinical edema usually involves more than one physiologic mechanism, it is not difficult to determine the predominant disturbance. Table 2 illustrates the physiologic mechanisms of clinical edema.

Physiologically, edema is an excessive accumulation of interstitial fluid. Clinically, it may be latent or manifest, and, by its nature, *localized* or *generalizing*. These terms, with the exception of *generalizing*, have been defined, and may be accepted. By *generalizing* edema is meant a condition in which edema is at first local in its appearance, but in which, as the process extends, edema will become general, causing anasarca. The degree of edema in any area is limited by tissue tension and the sites of its first appearance and later spread are partly determined by gravity.

CARDIAC EDEMA

Generalizing edema is an early manifestation of cardiac failure. It is usually considered to be evidence of inadequacy of the right ventricular musculature (back pressure theory). Peripheral edema may be accompanied by pulmonary edema in cases where there is simultaneous left ventricular failure. Actually, the genesis of cardiac edema may depend more on sodium retention[2,3,4] due to "forward cardiac failure" and renal constriction than on venous back pressure alone. The onset of cardiac edema is preceded by increases in blood and interstitial fluid volume. At times it is latent, and gravity causes it to become manifest earlier in the ambulatory than in the bedridden patient. The onset of latent edema may be predicted by careful daily weighing.

Cardiac edema usually appears first above the external malleolus and over the inner portion of the lower end of the tibia where the underlying bone renders pitting easy to detect. It tends to disappear with recumbency and is accentuated by any cardiad pressure, as from a garter. It is usually symmetrical and bilateral unless local disturbances, such as unilateral varicosities, complicate it.

TABLE 1

SYNDROMES IN WHICH EDEMA APPEARS

Types	Examples
GENERALIZING EDEMAS	
CARDIAC....................	Congestive cardiac failure.
NEPHRITIC..................	Acute and chronic glomerulonephritis and pyelonephritis; preeclampsia and eclampsia; toxic nephroses (CCl_4, Hg, etc.).
HEPATIC....................	Toxic and infectious hepatic disease; cirrhosis.
NUTRITIONAL................	Deficiencies of protein and vitamin.
ENDOCRINE..................	Premenstrual edema; desoxycorticosterone acetate overdose.
SODIUM EXCESS.............. (Absolute)	Excess sodium intake. Relative sodium excess is most common coincident factor in other generalizing edemas.
LOCALIZED EDEMAS	
VASCULAR	
Lymphatic.................. (Lymphedema)	Congenital lymphangitis; Milroy's disease; recurrent lymphangitis; filariasis.
Venous....................	Varicose veins; thrombophlebitis (acute and chronic); phlebothrombosis; phlebitis secondary to disease (polycythemia, brucellosis, typhoid, etc.).
Arterial...................	Thrombo-angiitis obliterans; Raynaud's disease.
EXTRA-VASCULAR	
Mechanical.................	Obstruction to lymphatic and venous flow; compression of main lymphatic and venous trunks by obesity, neoplasm, scars, fibrosis following radiation; direct invasion of nodes or lymph vessels by neoplasm.
	Pelvic or abdominal tumors (edema of lower extremities); mediastinal and axillary tumors (edema of upper extremities); hernia.
Traumatic.................	Local drug injection (venous sclerosis); local injury (stretching of extremity); fracture; vibration; foot strain; exposure to temperature changes (frostbite, burns, heat, immersion foot).
TOXIC	
Inflammatory and Allergic.....	Drugs (heavy metals, thiouracil); urticaria (specific or non-specific); trichinosis; sunburn; toxic erythema.
PSEUDO-EDEMAS	
LIPEDEMA	
MYXEDEMA	

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In bedridden patients cardiac edema tends to appear first in the sacral area and will shift its location with changes in sleeping positions. In orthopneic patients who sit forward in the chair it may be most marked in the anterior abdominal wall, scrotum, or vulva.

In contrast to hypoproteinemic edema, cardiac edema commonly and early involves serous cavities. The first cavity to be affected is often the right pleural space, possibly because of mechanical pressure from the dilated heart on the azygos vein. Severe cardiac edema involves all the subcutaneous tissue and serous cavities, the face being spared because of the coincident orthopneic position. Accumulations of serous fluids in the pleural spaces reduce lung volume and thus increase the respiratory embarrassment of cardiac failure. Postmortem studies reveal intense congestion and edema of all organs including the brain and leptomeninges. Cardiac edema pits readily and pitting disappears sooner than in the edema of glomerulonephritis, probably because venous engorgement and dilatation, as well as fluid excess, increase tissue volume. The edematous skin lacks the white appearance of renal edema, and there may be some associated cyanosis.

In long standing cardiac edema, thickening and hardening of the true skin may occur as a result of secondary inflammatory reactions and loss of elasticity. Such skin is thick and brawny, pits with difficulty and is somewhat reddened and irregularly pigmented. When pressure overcomes the limitation of the skin's resistance, actual rupture with

TABLE 2
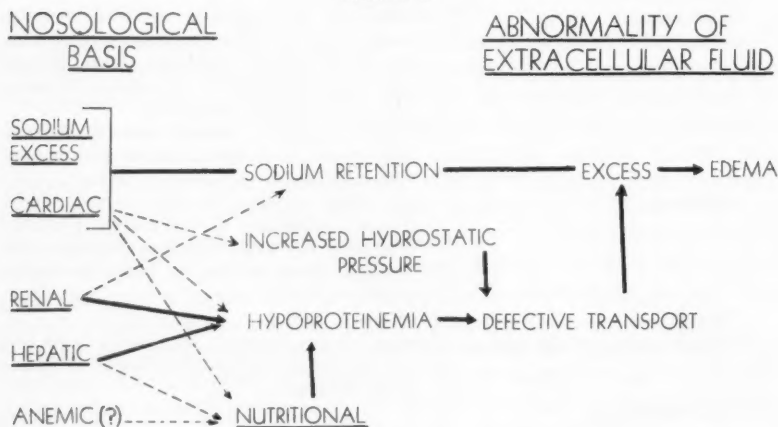
Solid arrows indicate primary, and dash arrows indicate secondary pathways of edema formation.

drainage may occur. This complication, however, is less common in recent years with better management of these patients and the use of the newer diuretics.

NEPHRITIC EDEMA

Nephritic edema has important differences in mechanism and distribution as it appears in acute hemorrhagic glomerulonephritis, acuet nephritis of insidious onset, or the nephrotic stage of glomerulonephritis.

The edema of acute hemorrhagic glomerulonephritis is less influenced by gravity than cardiac edema and manifests itself as a painless, pale, swelling, which pits with some difficulty. It is first noticed in the loose tissue of the orbit, in the eyelid, about the face, hands, scrotum, or vulva. It seems to originate largely from increased capillary permeability resulting from generalized vascular damage of the same type causing glomerular capillary damage. Nephritic edema is therefore in a sense inflammatory. The high protein content of the edema fluid tends to prevent its rapid absorption through the capillaries, and at the same time, salt retention, due to the renal lesion increases the tendency to fluid retention. Hypoproteinemic edema later supervenes.

Although acute nephritic edema may become generalized, it rarely assumes the degree seen with congestive failure. At times localized areas of edema occur which become important because of location. For instance, edema of the glottis may cause choking or asphyxia. Foci of edema in the cerebral cortex may account for convulsive seizures common in acute nephritis in children. The edema of the acute nephritic attack lasts only several days, or at the most a few weeks, and subsides without secondary complications. Cardiac failure is not uncommon during an acute nephritis and its appearance adds another mechanism to the production of nephritic edema.

Less commonly, nephritic edema first appears as a soft, pitting swelling of the ankles, shins, thighs, scrotum or vulva. In this form the onset of the disease is insidious rather than stormy. The edema is primarily hypoproteinemic and renal with sodium retention. The prognosis of the disease in this form is highly unfavorable.

The nephrotic phase of chronic glomerulonephritis, which at times is simulated by pyelonephritis, has a generalized edema as a persistent or recurrent feature. Certain cases, however, run their course without an obvious nephrotic phase, but rather with azotemia and renal insufficiency as an early, predominant feature. An interesting clinical observation is that because of increased sodium loss and because the plasma protein level rises, the edema of chronic nephritis lessens when uremia impends.

Hypoproteinemia is the major etiologic factor in chronic renal edema. The edema presents as a generalized, painless, pale swelling which may vary considerably in degree from day to day or week to week. At times massive renal edemas occur which may persist steadily for months with only minor variations in degree. In such cases the serous cavities are sometimes involved. Such massive edema predisposes to erysipeloid infections which may subside, leaving the skin thickened and reddened. Separation of the cutaneous elastic fibers results in the appearance of striae. As in cardiac anasarca, actual breaks in the skin surface occur with drainage and secondary infection. Terminally, with the onset of uremia, collections of fluid may follow the development of a sterile fibrinous pericarditis or pleurisy.

As in acute nephritis, sodium retention due to renal damage contributes to the edema. This contribution rather than changes of plasma protein might account for the unexplained, rapid variations in body weight and manifest edema. Cardiac failure also complicates the pattern.

Nephrosis is characterized by massive edema, hypoproteinemia, lipemia, and albuminuria. It is differentiated from the nephrotic stage of chronic glomerulonephritis by the absence of signs of renal irritation (red and white blood cells in the urinary sediment), and by its favorable course. The diagnosis of nephrosis should be made with greatest of caution in adults. This rare disease is somewhat more common in children. As in other edemas the skin is subject to erysipeloid infections. The course of nephrosis is sometimes complicated by abdominal pain, vomiting, and prostration which have been shown to be associated with the disappearance of amino acids from the blood.[5,6] These bouts which are frequently mistaken for attacks of pneumococcal peritonitis may be instantly cut short by intravenous administration of amino acid mixtures.

The third trimester of pregnancy is normally associated with an increase in plasma and interstitial fluid volumes which predispose to edema. Because of the weight of the gravid uterus, this edema is usually localized and manifest at the ankles. Eclamptogenic toxemias of pregnancy (pre-eclampsia and eclampsia) are characterized by generalizing edema which is especially manifest in the face, conjunctiva and hands. This edema and the coincident changes of renal function,[7] closely resemble that of acute glomerulonephritis. Because toxemia is often associated with prior malnutrition, however, hypoproteinemia is often a complicating factor.

HEPATIC EDEMA

Hepatogenous edema may be localized or generalizing. Ascites in the course of hepatic cirrhosis is a form of localized edema with peri-

toneal transudation dependent upon increased portal venous pressure. Generalized edema of hepatic origin may appear in any form of hepatic disease which is sufficiently extensive to impair the liver's ability to form new protein, and more particularly, serum albumin. It is, therefore, a form of hypoproteinemic edema which occurs as a complication of toxic and infectious hepatic disease and in hepatic cirrhosis. In none of these diseases is it commonly so extensive as to constitute a hazard in its own right.

NUTRITIONAL EDEMA

Edema may result from protein starvation or from protein lack with inadequate vitamin intake. Edema rarely results from vitamin deficiency alone.

Dietary protein deficiency can cause a sufficient decrease of serum protein to produce edema of a generalizing type. Such a deficiency may be absolute as in famine edema, or relative and due to increased metabolic demand (hyperthyroidism) or uncorrected protein loss (proteinuria, burns, severe eczema). Failure of gastrointestinal absorption, the result of local disease (gastro-colic fistula), or lack of utilization in the manufacturing process in the liver, may produce the same result. Protein deficiency is accentuated when the diet is low in calories as well as in proteins, because valuable stores of protein must then be burned for energy production. The failure of protein anabolism which characterizes states of damage or disease predisposes to hypoproteinemia and is only partially reversed by ingestion of large amounts of protein. One of the recently recognized complications of nutritional hypoproteinemia and edema is the tendency to disruption of wounds, particularly those of the abdominal wall.

Thiamine insufficiency may cause a mild edema of legs and ankles in association with the neuritic pain, weakness, and paresthesia due to the characteristic neurologic lesions. Gross edema appears rapidly in so-called wet beri-beri due to thiamine deficiency. The clinical picture is similar to that of cardiac decompensation from other causes. Probably the cardiac effect of thiamine deficiency is increased by antecedent cardiac damage. Diagnosis is made by therapeutic test with large doses of thiamine and other B vitamins. The heart is enlarged, particularly to the right. The electrocardiogram shows low voltage in the limb leads, T wave inversion, S-T depression and sinus bradycardia. Uncomplicated cases of wet beri-beri occur in the Orient. In this country, this form of edema is most often seen in chronic alcoholics whose disease is complicated by dietary insufficiency and gastrointestinal defect, and, in whom hepatic damage adds to the protein depletion.

EDEMA OF ENDOCRINE ORIGIN

A more or less generalized edema may be seen as an accompaniment of certain glandular dysfunctions. Premenstrual edema is regarded as due to renal retention of sodium under the influence of inadequately metabolized ovarian steriods.

Injection of desoxycorticosterone may result in generalized edema due to excessive retention of sodium ion. This reaction is seen in the treatment of Addison's disease or may be produced in normal individuals. It is relieved by administration of potassium, sodium restriction and water or ammonium chloride diuresis.

Certain hypothalamic states are associated with undue retention of fluid in the body which may be relieved by the use of benzedrine sulphate. It is possible that these states result from a disturbance of the water-regulating hormone of the posterior pituitary. Some edema may be found in the late stages of parathyroid disease with nephrolithiasis as the result of renal damage. Edema has also been noted to follow the administration of insulin to uncontrolled severe diabetics. This edema may be an expression of an insulin-induced water imbalance. Locally, it is occasionally seen in swelling of the lens, with temporary loss of sharp vision.

SODIUM EXCESS

Intake of sodium in excess of that which can be excreted by normal kidneys is uncommon and is usually seen only in patients given infusions of physiologic saline in large amounts causing an absolute sodium excess. More commonly, sodium excess is relative rather than absolute, being dependent upon the inability of functionally or structurally damaged kidneys to excrete a normal or even subnormal amount of dietary sodium.

VASCULAR EDEMA

Physiologically, edema of local origin is due to an abnormality in the movement of interstitial fluid which, while it causes local excess, cannot of its nature give rise to a great absolute increase in body fluid as a whole. Movement of interstitial fluid depends on the normal transport of blood and lymph. Local edema is therefore either blood-vascular or lymph-vascular in origin. In each category it is primary and the result of vascular disease alone, or secondary and due to extravascular causes. Primary blood-vascular edema is arterial or venous, the arterial forms being rare and probably not of themselves due to arterial activity.

Thus, edema in thrombo-angiitis obliterans is more commonly due to the associated thrombophlebitis than to arterial changes as such. The edema of Raynaud's disease is probably the result of local in-

flammatory change consequent on arterial spasm and tissue necrosis, and not the effect of arterial constriction alone.

Lymphedema is chronic in nature and commonly involves the lower extremities. In a small group of cases it is congenital and present at birth, or in a type known as lymphedema praecox, it appears at puberty. Milroy's disease also belongs to this group and is sometimes known as hereditary tropho-edema or lymphedema of a familial type. In contrast is the lymphedema resulting from recurrent lymphangitis which in the tropics may be caused specifically by filariasis.

Generally, lymphedema is gradual in onset. It may be unilateral or bilateral and is frequently not associated with any localized pain. Edema of this type pits easily and, in early stages, disappears promptly when the limb is elevated. At a late stage pitting becomes difficult due to infection and fibrosis. In the later stages of lymphedema the subcutaneous tissues become thick, hard, and folded, and ulceration may result with secondary infection. When this picture occurs, the name, elephantiasis, is frequently applied.

In contrast to lymphatic edema there are those edemas due primarily to involvement of the veins. Simple varicose veins are a common cause of edema of the lower extremities. The varices may or may not be associated with secondary thrombophlebitis. When phlebitis occurs, the edema is increased.

In the case of simple varices the edema is gradual in onset. The large superficial veins are readily detectable, but extent of visible varicosities is not an exact indication of the degree of venous incompetence. Color changes are marked, there being a dark rubor which approaches a cyanotic appearance. No unusual temperature changes are noted and the edema improves when the limbs are elevated. This type of edema is more severe at the end of a day.

Edema resulting from acute or chronic thrombophlebitis of the superficial or deep (phlebothrombosis) veins may occur in the absence of varicose veins, and usually with a history of acute onset, localized tenderness, redness, swelling, and frequently, with chill and fever. If the extent of the venous occlusion is not too great, no edema may develop. If several channels of return flow are involved, edema occurs when the patient stands for long periods. There is more discomfort and considerable fatigue of the leg muscles associated with this form of edema than with others. In later stages the skin becomes thickened and has a bright reddish, shiny appearance. Ulceration is common on the inner surface of the ankle. It is well to remember that thrombophlebitis may be secondary to several diseases including polycythemia, brucellosis, and typhoid fever.

EXTRA VASCULAR EDEMA

There are several important extra-vascular conditions resulting in secondary vascular disturbances which give rise to edema, particularly of the lower extremities. In the mechanical group are included those which interfere by pressure with lymphatic and venous return. Compression of the main lymphatic or venous trunks by fat tissue, neoplasm, postoperative scars, postradiation, fibrosis, direct invasion of the lymph nodes and vessels by neoplasm or surgical removal of these, may result in edema. Pelvic or abdominal tumors may thus cause edema of the lower extremities, and axillary or mediastinal tumors may similarly affect the arms. These masses are usually detectable by physical examination.

There are several important traumatic states which give rise to local edema. Edema of the hands particularly, is occasionally noted following intravenous injection of drugs which cause thrombosis. Traumatic phlebitis may occur following local injury. Repeated, severe stretching of the arms is an occasional cause. Instances of this form of traumatic thromboplebitis have been observed repeatedly in window washers. The "shelter edema" of the London Blitz resulted from compression of popliteal veins after long nights spent in deck chairs.

Local edema may also follow injury, particularly fracture. It may occur when fracture is not apparent, as from fracture of the small bones of the hands and feet. Chronic foot strain associated with mechanical foot defects is a common cause of mild localized edema. The immobilization which follows hemiplegia reduces blood and lymph flow and leads to minor degrees of local edema.

Edemas following frost bite, burns, and immersion foot are actually vascular and, in a degree, inflammatory. They are essentially secondary, however, to changes in temperature and environment. Diagnosis is simple because of the history of exposure.

A minor, but because of its frequency, differentially important form of edema, is that observed in women whose ankles and feet swell in summer. Such patients are usually those with well marked malleolar fat pads or a stocking type of subcutaneous fat deposit. The basis for this edema rises in vasodilation and increased transudation into an area of relatively low tissue tension, combined with high local venous pressure. Similar increased vascular permeability and blood flow are the probable causes of "heat edema" seen in the tropics or during heat waves in temporate climates. To a degree, heat edema is generalizing, for heat also tends to increase blood and interstitial fluid volume.

Certain chemical substances, particularly arsenicals, cause edema apparently as a result of capillary damage apart from or in association

with renal and hepatic lesion. Toxemia from certain infections, for example diphtheria, may act in a similar fashion.

A toxic type of cutaneous edema is that experimentally produced by the injection of hematoporphyrin in animals. The pigment sensitizes the skin so that subsequent exposure to light produces marked edematous swelling. Occasional instances have been noted in humans with congenital porphyria. Since these forms result from generalized changes they might be thought of as generalizing edemas. They merge imperceptibly, however, into the group of localized edemas caused by allergic sensitizations of all types, whose varied expressions and causes range from horse serum to hair dye, and from house cats to focal infections and rheumatic diatheses.

In the inflammatory group local edemas secondary to arthritis and local cellulitis are included. In the case of arthritis the swelling is localized to the affected joint areas, and signs of local tenderness, inflammation and restricted motion are present. Local edema may form distal to the joint, because of increased venous pressure from the site of arthritic inflammation. Trichinosis with its characteristic facial edema and eosinophilia is a member of this group.

Localized cellulitis secondary to trauma and infection may occur with resulting local edema. The area involved is centrally swollen, red, tender, and peripherally diffusely edematous. The onset is sudden with fever and leukocytosis.

PSEUDO-EDEMAS

So called lipedema, an abnormal local deposit of fat, frequently occurring about the ankles and the calves, may be confused with actual edema. It is nonpitting and nonpainful. During the summer especially it may cause true edema as noted above.

Myxedema of course is not a true edema, since the subcutaneous thickening is due to a myxomatous tissue deposit and not to increased intercellular fluid. Sluggish peripheral circulation, however, may result in an actual edema of the skin and subcutaneous tissue. Similarly, scleroderma and its congener, dermatomyositis, may be mistaken for edema. This confusion is not likely in the case of pseudohypertrophic muscular dystrophy.

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VON GIERKE'S GLYCOGEN DISEASE

Report of Two Cases

R. W. SCHNEIDER, M.D.

The purpose of this report is to present two cases of von Gierke's glycogen disease, to discuss its clinical characteristics, to review the present concept of the disease, and to digress somewhat on the mechanism of acidosis, particularly in children.

Von Gierke's glycogen disease is apparently limited to infancy and childhood. It is chronic, often with a familial tendency, and is characterized by an excessive accumulation of glycogen in various organs of the body, especially the liver, with subsequent enlargement of the affected organs. The stored glycogen, which cannot be mobilized,[1] seems to have normal chemical and physical properties and can be hydrolyzed by normal liver tissue. The liver may extend to the iliac crest, yet there is neither splenomegaly, ascites, nor jaundice. Appreciable impairment in liver function is not common. The fasting blood sugar is consistently low, usually without symptoms of hypoglycemia. Fasting acetonuria, lipemia, and hypercholesterolemia are not uncommon. Epinephrine may increase acetonuria but does not cause as great a rise in blood sugar levels as would occur normally.

The etiology and pathogenesis of the disease are not clear. It has been postulated that the fetal type of glycogen metabolism may persist into postnatal life,[2] since fetal glycogen does not disappear rapidly by spontaneous glycogenolysis and cannot be readily mobilized by the administration of epinephrine.[3] It has been suggested that the presence of diastatic ferment in the liver is necessary before epinephrine can release glucose from hepatic glycogen stores and that this enzyme is diminished or absent in this disease.[4] The chief organs affected are the liver, heart, kidneys, and brain, apparently in that sequence. Death

usually results from intercurrent infection. Occasionally, however, death may occur from cardiac decompensation, probably because deposition of glycogen within the myocardium impairs its function.

After death the liver glycogen, which ordinarily disappears in a few hours, persists for many days.[5] Chemical analyses have shown a greater than normal amount of glycogen in the organs affected.[3] The liver may contain areas of increased fibrosis.

CASE REPORTS

Case 1—An infant boy, aged 18 months, was first seen in consultation with Dr. Roscoe Leas two months after onset of symptoms. The illness began with four or five loose stools in one afternoon. The baby refused his supper as well as breakfast the following day. He then became drowsy and was admitted to the hospital in a comatose condition. Blood sugar level was 30 mg. per 100 ml. He was revived quickly with intravenous glucose and saline. Six weeks later he again became stuporous and semi-comatose; blood sugar levels were extremely low; and intravenous glucose caused a prompt return to consciousness. Blood count showed 4,100,000 erythrocytes with 71 per cent hemoglobin.

The child was bright, well nourished, and seemed normally active. Dental age was approximately normal. There was no goiter. The liver extended into the epigastrium, 3 cm. below the right costal margin in the region of the gallbladder and about 5 cm. below the tip of the xiphoid process (figure).

Urinalysis was normal except for the presence of acetone when blood sugar levels were very low and on the two occasions when the patient was stuporous. An oral galactose tolerance test after 15 Gm. galactose showed no sugar in the urine. Blood sugar level, which was 83 mg. per 100 ml. four hours after a generous breakfast, rose to 96 mg. per 100 ml. five minutes after administration of 3 minims epinephrine 1-1000 solution, and to 104 mg. per 100 ml. five minutes after a subsequent injection of 4 minims epinephrine 1-1000 solution. Blood cholesterol measured 128 and 179 mg. per 100 ml. on two occasions. On a low carbohydrate, high protein diet and 3 capsules lipocaic daily, the child had no attacks during the succeeding eight months.

Case 2—A girl, aged 7, had attacks since the age of 2 years consisting of staring, light-headedness, and pallor. These spells were accentuated by activity, occurred five to twenty times a day, and were often relieved by food.

The child was pale and appeared to be chronically ill. The muscles were poor in tone but seemed to be normal in strength. The liver was enlarged 4 fingers' breadth below the costal margin. Blood sugar level was 44 mg. per 100 ml. two and one half hours postprandial. A single dose oral glucose tolerance test using 50 Gm. glucose gave the following curve:

Hours	Fasting	½	1	2	3	4
Blood sugar mg./100 ml.	51	104	92	62	37	26

After giving 4 minims epinephrine 1-1000 solution the blood sugar level rose from 46 mg. per 100 ml. to 54 mg. per 100 ml. in fifteen minutes. An oral galactose tolerance

test after administration of 15 Gm. galactose showed no sugar in the urine. Bromsulfalein test of liver function revealed 28 per cent retention of dye in thirty minutes. Blood count showed 4,750,000 erythrocytes with 68 per cent hemoglobin. Urine was negative for acetone twice, neither test being after fasting or administration of epinephrine. Diastase levels on peripheral blood were normal. Permission for a liver biopsy was not granted. In two years symptoms were not altered by dietary manipulation, and the size of the liver did not appreciably change by the addition of lipocaic and lecithin. A brother, aged 4, had no enlargement of the liver or hypoglycemic tendency.

COMMENT

It is very probable that these cases are additional instances of von Gierke's disease. Since permission for liver biopsy was not granted, final proof of the diagnosis is lacking. Yet the finding of an enlarged liver in children without ascites, jaundice, or splenic enlargement, the presence of severe hypoglycemia, and the relative lack of response to subcutaneous administration of epinephrine seem more than presumptive evidence to

FIG.—Case 1, photograph with black lines showing upper and lower borders of the liver.

support the diagnosis. In one child acetone in the urine during fasting was additional evidence.

Apparently the principal metabolic defect in this disease is the liver's inability to convert glycogen into glucose. Therefore it is not difficult to understand the failure of epinephrine to raise blood sugar levels. This phenomenon is considered to be the most important diagnostic test clinically available. It is also not difficult to understand why acidosis appears readily, especially during fasting.

Shaw and Moriarity[6] demonstrated that children have a greater tendency toward acidosis than adults. They showed that children with epilepsy rapidly develop ketosis and acidosis while fasting. The acidosis was greatest in the third to the eighth day when hypoglycemia was present. Mirsky and Nelson[7] further demonstrated the increased susceptibility of children to acidosis after phlorhizination. After intravenous administration of phlorhizin a loss of 15 to 20 Gm. of sugar in the urine from a normal child and less than that from a diabetic child was followed by hypoglycemia and ketonuria, presumably because of a depletion of liver glycogen. The younger the child, the greater the susceptibility, apparently because of a smaller glycogen reserve. A more pronounced phlorhizin-induced glycosuria is necessary in adults before acidosis becomes manifest.

A different mechanism undoubtedly exists in von Gierke's disease. Here the liver glycogen is abundant, but being fixed, it is no more available for supplying metabolic demands for glucose than if no glycogen stores were present. Theoretically, the stimulus for oxidation of fatty acids and production of ketone bodies is the lack of available glycogen in the liver. If this be the case, it would explain the occurrence of acidosis in this disease.

The disease usually leads to death before the twentieth year. I have been unable to find any record of treatment which alters the usual progress of the disorder. A better understanding of its pathogenesis and treatment will probably come through study of enzymatic activity within the liver.

SUMMARY

In the two reported cases of von Gierke's glycogen disease the diagnosis was supported by the finding of hepatomegaly, severe hypoglycemia, anemia, acetonuria in one, and poor response to administration of epinephrine.

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THE FRANK E. BUNTS INSTITUTE

Tentative Program

Refresher Course on Treatment

Monday, February 25, 1946

9:00......Dr. W. E. Lower..........Prevention of Surgical Shock
9:30......Dr. A. C. Ernstene........Cardiac Emergencies
10:00......Dr. J. I. Kendrick.........Shoulder Disabilities
10:45......Dr. H. E. Harris..........Lempert Fenestration Operation
11:15......Dr. J. A. Dickson..........Fracture of the Neck of Femur
11:45......Dr. C. A. Resch...........Facial Pain of Dental Origin
12:30......Lunch
2:00......Dr. A. T. Bunts...........Spinal Cord Tumors
2:30......Dr. I. H. Page.............Shock I, General Problems
3:00......Dr. A. D. Ruedemann......Treatment by Beta Radium
3:45......Dr. R. J. F. Renshaw......Peptic Ulcer
4:15......Dr. C. L. Hartsock........Chronic Fatigue States
4:45......Dr. U. V. Portmann.......Cancer of the Breast
6:30......Dinner Meeting
　　　　　Dr. E. V. Cowdry..........Precancerous Lesions
　　　　　Washington University
　　　　　St. Louis

Tuesday, February 26, 1946

9:00......Dr. R. S. Dinsmore.........Treatment of Goiter
9:30......Dr. A. C. Corcoran.......Shock II, Renal Aspects
10:00......Dr. J. C. Root.............The Gastrointestinal Examination
10:45......Dr. W. J. Gardner.........Repair of Defects of the Skull
11:15......Dr. R. L. Haden...........Pernicious Anemia
11:45......Dr. C. R. K. Johnston......Status Asthmaticus
12:30......Lunch
2:00......Dr. W. J. Engel............Prostatic Hypertrophy
2:30......Dr. E. W. Netherton.......Eczema
3:00......Dr. T. E. Jones.............Treatment of Cancer
3:45......Dr. L. W. Diggs............Tests in Hemorrhagic Diseases
4:15......Dr. E. P. McCullagh......Endocrine Therapy in Menstrual Disorders
4:45......Dr. R. J. Kennedy..........Contact Lens
6:30......Dinner Meeting
　　　　　Fellows Reunion

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Wednesday, February 27, 1946

9:00......Dr. R. D. Taylor..........Pyelonephritis
9:30......Dr. George Crile, Jr.......Penicillin in Peritonitis
10:00.....Dr. F. A. LeFevre..........Coronary Artery Diseases
10:45.....Dr. P. M. Moore, Jr.......Dysphagia
11:15.....Dr. R. W. Schneider.......Sterility due to Polycystic Ovaries
11:45.....Dr. R. H. McDonald.......Parenteral Fluid Therapy
12:30.....Lunch
2:00......Dr. John Tucker..........Headache
2:30......Dr. W. J. Zeiter..........Physical Medicine
3:00......Dr. C. C. Higgins.........Renal Lithiasis
3:45......Dr. Otto Glasser.........Dosimetry of X-rays
4:15......Dr. E. N. Collins.........Chronic Ulcerative Colitis
4:45......Dr. C. R. Hughes.........Beryllium Poisoning

REGISTRATION BLANK

......................................, 1945

The Frank E. Bunts Institute
Cleveland Clinic
East 93rd Street and Euclid Avenue
Cleveland 6, Ohio

Gentlemen:

Please register me for "The Refresher Course on Treatment" which is to be given February 25, 26, 27, 1946.

I am sending check for $5.00, and the remainder of the fee, $5.00, will be paid on Registration, February 25.

NOTE: Checks should be made payable to the Frank E. Bunts Institute and sent to A. D. Ruedemann, M.D., Cleveland Clinic, Cleveland, Ohio.

Name...

Address......................................

Medical School and
date of graduation...............................

Mail registration blank to Dr. A. D. Ruedemann, Cleveland Clinic, East 93rd Street and Euclid Avenue, Cleveland 6, Ohio.